PATENT COOPERATION TREA . Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 07 February 2000 (07.02.00)	
International application No. PCT/US99/11277	**Applicant's or agent's file reference** 4239-52215
International filing date (day/month/year) 21 May 1999 (21.05.99)	**Priority date** (day/month/year) 21 May 1998 (21.05.98)
Applicant WIENER, Stephen, M. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

20 December 1999 (20.12.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. Forax
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

3090585

E.K

PATENT COOPERATION TREATY

PCT

09/700999

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
4239-52215		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/11277	21/05/1999	21/05/1998

Applicant

THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of Invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   METHOD FOR PRESSURE MEDIATED SELECTIVE DELIVERY OF THERAPEUTIC SUBSTANCES AND CANNULA

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 19

   [ ] as suggested by the applicant.

   [X] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/11277

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-60, 70-78
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/11277

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Add the following to the abstract after the last line ("...is desired."):

The access device comprises a cannula with a wall piercing tracar within the lumen. Two axially spaced inflatable balloons engage the wall securing the cannula and sealing the puncture site. A catheter equipped with an occlusion balloon is guided through the cannula to the location where the therapeutic substance is to be delivered.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11277

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M25/02 A61B17/34 A61M25/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M A61B A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 3 952 742 A (TAYLOR DUANE F) 27 April 1976 (1976-04-27) figures 1,2	61,63,66 62,64, 65,67-69
Y	US 5 250 040 A (PARKS ET AL.) 5 October 1993 (1993-10-05) abstract; figures 8-12	62,64,65
Y	US 5 484 412 A (PIERPONT) 16 January 1996 (1996-01-16) abstract; figures 1-5	67-69
X	US 5 211 624 A (CINBERG ET AL.) 18 May 1993 (1993-05-18) abstract; figures 1-3	61,63,66

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 1999	01/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Michels, N

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11277

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 15655 A (MEDICAL INNOVATIONS CORP.) 21 July 1994 (1994-07-21) abstract; figures 1-6	61-69
A	FR 2 659 239 A (LEFEBVRE) 13 September 1991 (1991-09-13)	
A	EP 0 321 614 A (CALDERON) 28 June 1989 (1989-06-28)	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/11277

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3952742 A	27-04-1976	NONE	
US 5250040 A	05-10-1993	US 5234417 A	10-08-1993
		WO 9109643 A	11-07-1991
		US 5399173 A	21-03-1993
US 5484412 A	16-01-1996	WO 9721460 A	19-06-1997
		EP 0871511 A	21-10-1998
US 5211624 A	18-05-1993	AU 3655593 A	19-07-1993
		US 5354270 A	11-10-1994
		WO 9311716 A	24-06-1993
WO 9415655 A	21-07-1994	AU 677286 B	17-04-1997
		AU 5964094 A	15-08-1994
		CA 2151259 A	21-07-1994
		EP 0683684 A	29-11-1995
		US 5458583 A	17-10-1995
FR 2659239 A	13-09-1991	NONE	
EP 0321614 A	28-06-1989	AT 87489 T	15-04-1993
		US 4714460 A	22-12-1987

PATENT COOPERATION TREATY

PCT

CORRECTED VERSION

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

15

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4239-52215		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/11277	21/05/1999	21/05/1998
International Patent Classification (IPC) or national classification and IPC A61M25/02		
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

CORRECTED VERSION

Date of submission of the demand	Date of completion of this report
20/12/1999	12.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Abraham, V Telephone No. +49 89 2399 7463

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/11277

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-42	as originally filed

Claims, No.:

1-50	as received on	14/01/2000	with letter of	12/01/2000

Drawings, sheets:

1/28-28/28	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-33,43-50.

because:

☒ the said international application, or the said claims Nos. 1-33,43-50 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-33,43-50.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	35,37,38,40-42
	No:	Claims	34,36,39
Inventive step (IS)	Yes:	Claims	40-42
	No:	Claims	35,37,38
Industrial applicability (IA)	Yes:	Claims	34-42
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:
D1: US-A-3 952 742 (TAYLOR DUANE F) 27 April 1976
D2: US-A-5 250 040 (PARKS ET AL.) 5 October 1993
D3: US-A-5 484 412 (PIERPONT) 16 January 1996

III

1. No search report has been established for claims 1-33 and 43-50. Therefore, the question whether the claimed invention meets the requirements of Article 33(2)-(4) PCT will not be examined in respect of these claims.

   However, the following general comments are made with regard to the amended method claims filed with letter dated 12.01.2000:

   - Even after the amendments the claimed method implicitly includes the surgical step of inserting the infusion means into the targeted organ. Therefore, contrary to the applicant's point of view, the method claims still fall under the regulations of Rule 39.1(iv) and Rule 67.1(iv)PCT.

   - In the light of the description the step of inserting the infusion means is essential for the claimed method. The deletion of this essential surgical step may lead to a generalisation which extends beyond the content of the application as filed, contrary to Article 19(2) PCT.

V

1. As far as being understood in the light of the description (see VIII 1 below) the subject-matter of claims 34, 36 and 39 does not meet the requirement of Article 33(2) PCT for lack of novelty:

1.1 Document D1 which is at present considered to represent the most relevant prior art discloses the following:

An access device (10) for targeted delivery of therapeutic or diagnostic agents (column 1, lines 58-60) comprising:
an elongated cannula (12) having a wall, proximal and distal ends. and a lumen configured to contain a sharp tipped trochar (14)...and first and second balloons

(22,24) spaced axially along the cannula at positions such that, when the cannula is inserted through the wall of the desired body organ and the balloons are inflated, the first balloon engages an inner face of the organ and the second balloon engages an outer face of the organ, holding the distal end of the cannula in position within the hollow space inside the organ and substantially sealing against leaks (Fig. 4).

The device further comprises inflation ports (34, 36) positioned at or near the proximal end of the cannula for inflating the first and second balloons (Fig. 1).

The invasive access device of D1 implicitly consists of bio-compatible material.

2. The subject-matter of claims 35, 37 and 38 does not meet the requirement of Article 33(3) PCT for lack of an inventive step.

2.1 The additional feature of claim 35 has already been employed for the same purpose in a similar access device, see document D2, column 1, lines 45-47, Fig. 1A. It would be obvious to the person skilled in the art, namely when the same result of providing a drainage line is to be achieved, to apply this feature with corresponding effect to a device according to document D1, thereby arriving at a device according to claim 35.

2.2 The additional features of claims 37 and 38 have also been employed for the same purpose in the access device according to document D2 (Fig. 1A, 40). It would be obvious to the person skilled in the art, namely when the same result of closing the cannula is to be achieved, to apply these features with corresponding effect to a device according to document D1, thereby arriving at a device according to claims 37 and 38.

3. The problem to be solved by the additional catheter as defined in claim 40 is regarded in providing a closed chamber within the targeted body lumen.

From the prior art balloon catheters with the capability of occluding a body lumen are generally known (see for example D3). However, the combination of such a balloon catheter with the cannula as defined in claim 34 in order to provide a

closed chamber within the targeted body lumen is neither known from, nor rendered obvious by, the available prior art. Claim 40 therefore meets the requirements of Article 33(2)-(4) PCT.

4. Claims 41 and 42 are dependent on claim 40 and as such also meet the requirements of Article 33(2)-(4) PCT.

VII

1. A new independent claim should have been drafted in the two part form in accordance with Rule 6.3(b) PCT, with those features known in combination from D1 being placed in the preamble (Rule 6.3(b)(i) PCT) and with the remaining features being included in a characterising part (Rule 6.3(b)(ii) PCT).

2. The features of the claims should have been provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

3. According to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 should have been mentioned in the description and these documents should have been identified therein.

4. The units [inch] and [mm Hg] employed throughout the description and in the drawings should have been additionally expressed in terms of the units stipulated by Rule 10.1(a) PCT.

VIII

1. Claim 34 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The following functional statements do not enable the skilled person to determine which technical features are necessary to perform the stated functions:

"**first and second balloons spaced** axially along the cannula at positions **such that**, when the cannula is inserted through the wall of the desired body organ and the balloons are inflated, the first balloon engages an inner face of the organ and the second balloon engages an outer face of the organ, holding the distal end of the cannula in position within the hollow space inside the organ and substantially

sealing against leaks."

The position of the balloons on the cannula is defined with respect to the desired body organ. Due to the biological variation of organ wall thickness and, additionally, due to the plurality of desired organs disclosed (see page 2, lines 7-9) such a definition is unclear (see also PCT Guidelines III 4.8a).

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

NOONAN, William D.
NOONAN, William, D.;
Klarquist, Sparkman, Campbell, Leig
LP;
One World Trade Center, Suite 1600
Portland, OR 97204
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	12.09.2000
Applicant's or agent's file reference 4239-52215	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/11277	21/05/1999	21/05/1998

Applicant
THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Edel, M Tel.+49 89 2399-2426

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4239-52215		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/11277	21/05/1999	21/05/1998
International Patent Classification (IPC) or national classification and IPC A61M25/02		
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/12/1999	12.09.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Abraham, V Telephone No. +49 89 2399 7463

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/11277

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-42	as originally filed			

Claims, No.:

1-50	as received on	14/01/2000	with letter of	12/01/2000

Drawings, sheets:

1/28-28/28	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-33,43-50.

because:

☒ the said international application, or the said claims Nos. 1-33,43-50 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-33,43-50.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	35,37,38,40-42
	No:	Claims	34,36,39
Inventive step (IS)	Yes:	Claims	40-42
	No:	Claims	35,37,38
Industrial applicability (IA)	Yes:	Claims	34-42
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:
D1: US-A-3 952 742 (TAYLOR DUANE F) 27 April 1976
D2: US-A-5 250 040 (PARKS ET AL.) 5 October 1993
D3: US-A-5 484 412 (PIERPONT) 16 January 1996

III

1. No search report has been established for claims 1-33 and 43-50. Therefore, the question whether the claimed invention meets the requirements of Article 33(2)-(4) PCT will not be examined in respect of these claims.

   However, the following general comments are made with regard to the amended method claims filed with letter dated 12.01.2000:

   - Even after the amendments the claimed method implicitly includes the surgical step of inserting the infusion means into the targeted organ. Therefore, contrary to the applicant's point of view, the method claims still fall under the regulations of Rule 39.1(iv) and Rule 67.1(iv)PCT.

   - In the light of the description the step of inserting the infusion means is essential for the claimed method. The deletion of this essential surgical step may lead to a generalisation which extends beyond the content of the application as filed, contrary to Article 19(2) PCT.

V

1. As far as being understood in the light of the description (see VIII 1 below) the subject-matter of claims 34, 36 and 39 does not meet the requirement of Article 33(2) PCT for lack of novelty:

1.1 Document D1 which is at present considered to represent the most relevant prior art discloses the following:

An access device (10) for targeted delivery of therapeutic or diagnostic agents (column 1, lines 58-60) comprising:
an elongated cannula (12) having a wall, proximal and distal ends. and a lumen configured to contain a sharp tipped trochar (14)...and first and second balloons

(22,24) spaced axially along the cannula at positions such that, when the cannula is inserted through the wall of the desired body organ and the balloons are inflated, the first balloon engages an inner face of the organ and the second balloon engages an outer face of the organ, holding the distal end of the cannula in position within the hollow space inside the organ and substantially sealing against leaks (Fig. 4).

The device further comprises inflation ports (34, 36) positioned at or near the proximal end of the cannula for inflating the first and second balloons (Fig. 1).

The invasive access device of D1 implicitly consists of bio-compatible material.

2. The subject-matter of claims 35, 37 and 38 does not meet the requirement of Article 33(3) PCT for lack of an inventive step.

2.1 The additional feature of claim 35 has already been employed for the same purpose in a similar access device, see document D2, column 1, lines 45-47, Fig. 1A. It would be obvious to the person skilled in the art, namely when the same result of providing a drainage line is to be achieved, to apply this feature with corresponding effect to a device according to document D1, thereby arriving at a device according to claim 35.

2.2 The additional features of claims 37 and 38 have also been employed for the same purpose in the access device according to document D2 (Fig. 1A, 40). It would be obvious to the person skilled in the art, namely when the same result of closing the cannula is to be achieved, to apply these features with corresponding effect to a device according to document D1, thereby arriving at a device according to claims 37 and 38.

3. The problem to be solved by the additional catheter as defined in claim 40 is regarded in providing a closed chamber within the targeted body lumen.

From the prior art balloon catheters with the capability of occluding a body lumen are generally known (see for example D3). However, the combination of such a balloon catheter with the cannula as defined in claim 34 in order to provide a

closed chamber within the targeted body lumen is neither known from, nor rendered obvious by, the available prior art. Claim 40 therefore meets the requirements of Article 33(2)-(4) PCT.

4. Claims 41 and 42 are dependent on claim 40 and as such also meet the requirements of Article 33(2)-(4) PCT.

VII

1. A new independent claim should have been drafted in the two part form in accordance with Rule 6.3(b) PCT, with those features known in combination from D1 being placed in the preamble (Rule 6.3(b)(i) PCT) and with the remaining features being included in a characterising part (Rule 6.3(b)(ii) PCT).

2. The features of the claims should have been provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

3. According to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 should have been mentioned in the description and these documents should have been identified therein.

4. The units [inch] and [mm Hg] employed throughout the description and in the drawings should have been additionally expressed in terms of the units stipulated by Rule 10.1(a) PCT.

VIII

1. Claim 34 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The following functional statements do not enable the skilled person to determine which technical features are necessary to perform the stated functions:

"**first and second balloons spaced** axially along the cannula at positions **such that**, when the cannula is inserted through the wall of the desired body organ and the balloons are inflated, the first balloon engages an inner face of the organ and the second balloon engages an outer face of the organ, holding the distal end of the cannula in position within the hollow space inside the organ and substantially

sealing against leaks."

The position of the balloons on the cannula is defined with respect to the desired body organ. Due to the biological variation of organ wall thickness and, additionally, due to the plurality of desired organs disclosed (see page 2, lines 7-9) such a definition is unclear (see also PCT Guidelines III 4.8a).

We claim:

I 1. A method for delivery of a therapeutic or diagnostic agent, the method comprising:

administering a fluid comprising a therapeutic or diagnostic agent to a preselected region within an organ, by forming a substantially closed chamber within or adjacent the organ, and delivering the fluid at a preselected pressure, flow rate or volume of administration to direct delivery of the fluid to the preselected region.

2. The method of claim 1, wherein the preselected region is a histological layer of the organ.

3. The method of claim 2, wherein the histological layer is selected from the group consisting of (a) an epithelial or subepithelial layer; (b) an endothelial or subendothelial layer; (c) a serosa or subserosal layer; and (d) an adventitial or subadventitial layer.

4. The method of claim 1, wherein the organ comprises a blood vessel or a hollow viscus, and an interior volume of the blood vessel or hollow viscus is isolated to control the predetermined pressure, flow rate or volume of administration.

5. The method of claim 1, wherein an external area of the organ is isolated to control the preselected pressure, flow rate, or volume of administration.

6. The method of claim 1 further comprising:

forming a closed chamber within the organ by forming a closed chamber within a hollow organ space within the organ or forming a closed chamber around the organ or a portion of the organ; and

administering the fluid into the hollow organ space or the chamber around the organ; and

controlling at least one of a pressure, a flow rate, and a volume of the administration of the fluid in the closed chamber such that the agent is selectively delivered either to a region deep to a superficial layer, or substantially only to a superficial layer surrounding the hollow organ space, or is selectively delivered to the external surface of the organ, or substantially only to a layer deep to the external surface of the organ.

7. The method of claim 1 wherein controlling at least one of the pressure, the flow rate, and the volume comprises determining a threshold pressure for disruption of microanatomic barriers that inhibit subepithelial delivery of the agent, and (a) administering the fluid at a pressure below the threshold pressure when delivery only to the superficial layer is desired, or (b) administering the fluid at a pressure at or above the threshold pressure when delivery to the region deep to the superficial layer is desired.

8. The method of claim 1, wherein controlling at least one of the pressure, the flow rate, and the volume comprises controlling a liquid pressure.

9. The method of claim 8, wherein controlling the liquid pressure comprises controlling a pressure gradient within or across the organ.

10. The method of claim 8, wherein controlling the liquid pressure comprises administering

the liquid at a constant pressure.

11. The method of claim 1, wherein forming a closed chamber within a hollow organ space comprises accessing the hollow organ space, substantially occluding an outlet therefrom, and draining the hollow organ space to remove bodily fluids that may interfere with the action of the therapeutic or diagnostic agent.

12. The method of claim 11 further comprising, after draining the hollow organ space, rinsing the hollow organ space so as to remove traces of bodily fluids that may interfere with the action of the therapeutic or diagnostic agent.

13. The method of claim 6, further comprising, after administering the fluid comprising the therapeutic or diagnostic agent, draining the hollow organ space to remove the agent.

14. The method of claim 13, further comprising, after draining the hollow organ space to remove the therapeutic or diagnostic agent, rinsing the hollow organ space to remove traces of the agent.

15. The method of claim 6 wherein the superficial layer consists of epithelial cells surrounding the hollow organ space and the area deep to the superficial layer consists of areas deep to said epithelial cells.

16. The method of claim 1 wherein controlling at least one of the pressure, the flow rate, and the volume comprises substantially occluding an outlet from a hollow organ space, and varying the flow rate or volume so as to obtain a desired pressure.

17. The method of claim 1 wherein controlling at least one of the pressure, the flow rate, and the volume comprises administering a specified volume in the closed chamber.

18. The method of claim 1, further comprising predetermining a threshold pressure, flow rate or volume for delivery to a selected anatomic or microanatomic site, and controlling at least one of a pressure, flow rate or volume to direct delivery of the agent to the selected site.

19. The method of claim 18 wherein predetermining a threshold further comprises administering a test fluid into the closed chamber at a given flow rate and measuring a peak pressure at which delivery to a region deep to the superficial layer commences, and wherein controlling at least one of the pressure, the flow rate or the volume comprises administering the fluid (1) as part of a fluid flow into the closed chamber during which the peak pressure is not exceeded, when selective delivery only to a superficial layer is desired, or (2) as part of a fluid flow into the closed chamber during which the peak pressure is equaled or exceeded, when selective delivery to a region deep to the superficial layer is desired.

20. The method of claim 1 further comprising administering a test fluid into the hollow organ space multiple times, at a given flow rate, and measuring respective multiple peak pressures at which delivery to a region deep to the superficial layer commences, and wherein controlling at least one of the pressure, the flow rate, and the volume comprises administering the fluid comprising the therapeutic or diagnostic agent (1) as part of a fluid flow during which the last-

measured peak pressure is not exceeded, when selective delivery only to a superficial layer is desired, or (2) as part of a fluid flow during which the last-measured peak pressure is equaled or exceeded, when selective delivery to a region deep to the superficial layer is desired.

21. The method of claim 1 wherein the closed chamber comprises a hollow organ space, and controlling at least one of the pressure, the flow rate, and the volume comprises administering the fluid comprising the therapeutic or diagnostic agent at a pressure only slightly above a normal physiologic intralumenal pressure in the hollow organ space, at a pressure sufficient to achieve selective delivery substantially only to the superficial layer.

22. The method of claim 21 wherein the fluid administered slightly above a normal physiologic intralumenal pressure is administered at a pressure no more than about 2-5 mm Hg above the normal physiologic intralumenal pressure in the hollow organ space.

23. The method of claim 6 wherein the hollow organ space comprises a non-vascular interior of a hollow viscus.

24. The method of claim 6 wherein the hollow organ space comprises the lumen of a duct.

25. The method of claim 1 wherein the closed chamber comprises a hollow organ space, and the method further comprises isolating a portion of the hollow organ space within the body to form the substantially closed chamber.

26. The method of claim 25 wherein isolating the portion of the hollow organ space comprises occluding a duct draining the organ.

27. The method of claim 26 wherein the isolated portion of the hollow organ space comprises the hepatobiliary tract.

28. The method of claim 25 wherein the isolated portion of the hollow organ space comprises the gall bladder and/or ducts of the hepatobiliary tract.

29. The method of claim 25 wherein the isolated portion of the hollow organ space comprises hepatic bile ducts or at least a portion of intestine.

30. The method of claim 7 wherein controlling at least one of the pressure, the flow rate and the volume comprises administering the fluid above the threshold pressure to the region deep to the superficial layer.

31. The method of claim 30 wherein the fluid is administered above the threshold pressure, at a sufficient pressure to drive the therapeutic or diagnostic agent into a parenchyma of the organ.

32. The method of claim 25 wherein the pressure drives the therapeutic or diagnostic agent into the parenchyma of the liver.

33. The method of claim 1 wherein the therapeutic or diagnostic agent comprises at least one of a chemotherapy agent, a pro-inflammatory agent, an anti-inflammatory agent, and a genetic vector.

34. The method of claim 6 wherein the therapeutic or diagnostic agent comprises a genetic vector, and at least one of a pressure, a flow rate, and a volume of the administration of the fluid is

controlled such that selective delivery of the genetic vector is made substantially only to superficial cells adjoining the hollow organ space.

35. The method of claim 6 wherein the hollow organ space comprises at least a portion of the hepatobiliary tract, the therapeutic or diagnostic agent comprises a genetic vector, and at least one of a pressure, a flow rate, and a volume of the administration of the fluid is controlled such that selective delivery is made to hepatocytes near the hollow organ space.

36. The method of claim 6 wherein the hollow organ space is in an organ that includes a neoplasm, and the agent comprises an anti-neoplastic agent or a pro-inflammatory cytokine.

37. The method of claim 6 wherein the hollow organ space comprises:

(a) a portion of the hepatobiliary system adjacent to or involved with hepatic fibrosis, primary biliary cirrhosis or sclerosing cholangitis, and the therapeutic or diagnostic agent comprises an anti-inflammatory agent; or

(b) a portion of intestine affected with Crohn's disease, and the therapeutic or diagnostic agent comprises an anti-inflammatory agent for delivery at a sufficient pressure to introduce the therapeutic or diagnostic agent to a subepithelial lamina propria of the intestinal wall; or

(c) a portion of hepatobiliary tract, the superficial layer comprises epithelial cells lining the hepatobiliary tract, and the region deep to the superficial layer comprises at least one of sinusoids of the liver, Space of Disse, lamina propria, and smooth muscle cells of the gall bladder; or

(d) a portion of the pancreas affected by pancreatic adenocarcinoma and the the therapeutic agent comprises an anti-neoplastic agent or a pro-inflammatory agent or an agent that promotes the formation of blood vessels; and the agent is delivered to either the epithelial cells or subepithelial cells or both; or

(e) a portion of the esophagus affected by esophageal carcinoma and the therapeutic agent comprises an anti-neoplastic agent or a pro-inflammatory agent; or

(f) a portion of the prostate gland affected by prostatic carcinoma and the therapeutic agent comprises an anti-neoplastic agent or a pro-inflammatory agent; or

(g) a portion of the urinary bladder affected by carcinoma and the therapeutic agent comprises an anti-neoplastic agent or a pro-inflammatory agent delivered to either the superficial epithelial cells, the lamina propria, any or all of the circular and longitudinal muscle layers, and/or the serosa.

38. The method of claim 1, wherein the agent comprises spherical particles having a diameter of no more than about 500 nm.

39. The method of claim 1, wherein the agent is a nonparticulate agent.

40. The method of claim 1, wherein the fluid is administered at a flow rate of 0.066-960 µl/sec.

41. The method of claim 1, wherein the fluid is administered at a flow rate of less than 1000 µl/sec.

42. The method of claim 41, wherein the fluid is administered at a pressure of no more than about 500 mm Hg.

43. The method of claim 42, wherein the fluid is administered at substantially constant pressure.

44. The method of claim 43, wherein the organ is non-vascular, and the fluid is administered at a substantially constant pressure of about 5-100 mm Hg.

45. The method of claim 43, wherein the organ is vascular, and the fluid is administered at a substantially constant pressure of about 5-400 mm Hg.

46. The method of claim 1, wherein pressure is controlled, and the method further comprises substantially constant monitoring of the pressure during administration of the fluid.

47. The method of claim 1, further comprising administering a pharmacological substance that improves opening of tight junctions.

48. The method of claim 1, wherein the organ is a hollow viscus, and the method further comprises partially filling the hollow viscus with an inflatable space occupier before administering the fluid.

49. The method of claim 1, wherein the pressure is controlled by creating a pressure gradient in a solid portion of the organ, wherein the pressure gradient is preselected to deliver the agent to the predetermined region.

50. The method of claim 49, wherein the pressure gradient is highest inside the organ.

51. The method of claim 49, wherein the pressure gradient is highest outside the organ.

52. A method of determining a threshold pressure for selective administration of a therapeutic or diagnostic substance, the method comprising:

isolating a hollow organ space;

one or more times, introducing a test fluid into the hollow organ space at a preselected flow rate; and

one or more times, administering a test solution to determine a pressure at which leakage across epithelial or endothelial tight junctions occurs; and

administering a liquid including the therapeutic or diagnostic substance by introducing the liquid into the isolated hollow organ space, during which the pressure is not exceeded with the purpose of preferentially delivering the substance to an epithelial layer of the hollow organ space, or during which the peak pressure is exceeded with the purpose of preferentially delivering the substance to a subepithelial layer of the hollow organ space.

53. The method of claim 52 wherein administering the liquid comprises administering the liquid at a pressure that at least temporarily exceeds the peak pressure, with the purpose of preferentially delivering the substance to the subepithelial or subendothelial layer.

54. A method of determining the delivery pressure for selective administration of a

therapeutic or diagnostic substance, the method comprising:

isolating a hollow organ space;

one or more times, introducing a test fluid into the hollow organ space at a preselected approximately constant pressure;

one or more times, measuring the infusion rate of the administered fluid as the test fluid is introduced; and

administering a liquid including a test solution into the hollow organ space and determining a flow rate at which paracellular leakage across endothelial or epithelial tight junctions occurs.

55. The method of claim 52 wherein the test fluid has a viscosity substantially similar to that of the liquid containing the therapeutic or diagnostic substance.

56. The method of claim 52 wherein isolating the hollow organ space comprises introducing a catheter into the hollow organ space, and substantially sealing one or more outlets from the hollow organ space.

57. A method of delivering a therapeutic or diagnostic substance, the method comprising:

introducing a flexible catheter into an organ lumen lined with polar epithelial cells; and

infusing a therapeutic or diagnostic substance through the catheter into the organ lumen under preselected, controlled pressure conditions at which the therapeutic or diagnostic substance is delivered substantially only to apical surfaces of the epithelial cells and substantially not to any subepithelial regions.

58. The method of claim 57 wherein the organ lumen is an hepatic or biliary duct and the therapeutic or diagnostic substance is infused at a pressure sufficient to deliver the agent substantially only to cholangiocytes lining the hepatic or biliary duct.

59. The method of claim 57, further comprising infusing the therapeutic or diagnostic substance into the organ lumen under pre-selected, controlled pressure conditions at which the therapeutic or diagnostic substance is delivered not only to apical surfaces of the epithelial cells but also to subepithelial regions including basal surfaces of the epithelial cells.

60. The method of claim 59 wherein the body lumen is an hepatic or biliary duct, and the therapeutic or diagnostic substance is infused at a sufficient pressure to deliver the agent to cholangiocytes, hepatocytes, or both.

61. An access device for targeted delivery of therapeutic or diagnostic agents, the access device comprising:

an elongated cannula having a wall, proximal and distal ends, and a lumen configured to contain a sharp-tipped trochar for penetrating a wall of a desired body organ having a hollow space therein; and

first and second balloons spaced axially along the cannula at positions such that, when the cannula is inserted through the wall of the desired body organ and the balloons are inflated, the first balloon engages an inner face of the organ and the second balloon engages an outer face of the

organ, holding the distal end of the cannula in position within the hollow space inside the organ and substantially sealing against leaks.

62. The access device of claim 61 further comprising a drainage line communicating with a drainage inlet distal to the first and second balloons.

63. The access device of claim 61 further comprising inflation ports positioned at or near the proximal end of the cannula for inflating the first and second balloons.

64. The access device of claim 61 further comprising a selectively removable occluder that selectively closes the cannula.

65. The access device of claim 64 wherein the occluder comprises a cannula cap.

66. The access device of claim 61 wherein the cannula consists of bio-compatible materials.

67. The access device of claim 61 further comprising a flexible catheter having an exterior and a distal tip, the catheter being capable of insertion through the cannula, the catheter including an inflatable balloon near its distal tip, that upon inflation is capable of occluding a duct communicating with the desired body organ into which organ the tubular body is introduced.

68. The access device of claim 67, wherein the catheter comprises multiple lumens, and one of the multiple lumens communicates with the exterior of the catheter proximally of the inflatable balloons.

69. The access device of claim 67 wherein at least one of the multiple lumens communicates with the exterior of the catheter distally of the inflatable balloon.

I 70. A method of accessing an interior of a gall bladder, the method comprising;

inserting a trochar into a cannula having first and second peripheral inflatable cuffs;

introducing the trochar, together with the cannula, at an insertion site through the wall of the gall bladder and advancing the cannula into the gall bladder such that the first inflatable cuff enters the gall bladder but the second inflatable cuff does not;

inflating the first cuff so that it abuts an inner face of the gallbladder around the insertion site; and

inflating the second cuff so that it abuts an outer face of the gallbladder around the insertion site.

I 71. A method of delivering a therapeutic or diagnostic agent to a selected portion of the liver, the method comprising;

introducing a catheter into a hepatic duct draining the selected portion of the liver;

occluding the duct normograde from a distal tip of the catheter; and

infusing the therapeutic or diagnostic agent through the catheter into at least a portion of the selected portion of the liver at a preselected pressure that has been determined to move the agent out of the duct and into the periductular tissue.

72. The method of claim 71, wherein the hollow gastrointestinal viscus is an hepatobiliary duct, and the periductular tissue is hepatic tissue.

73. The method of claim 71 wherein the viscus has a vascular flow exiting therefrom, and the method further comprises at least partially occluding the vascular flow exiting from the viscus such that uptake of the agent in the viscus is enhanced.

74. The method of claim 73, wherein the vascular flow is venous or lymphatic flow.

75. The method of claim 71, wherein the viscus is at least a portion of at least one of a gallbladder, a pancreas, a liver, a bile duct, an intestine, a stomach, an esophagus, a trachea, a bronchus, a fallopian tube, a uterus, a cervix, a vagina, a duct of a parotid gland, a duct of a salivary gland, a prostate gland, a ureter, a urinary bladder, and a kidney of the patient.

76. The method of claim 71, further comprising introducing into the viscus a pharmacological substance that tends to open tight junctions between epithelial cells.

77. A method of introducing a therapeutic or diagnostic agent into a biological structure within the body, comprising introducing the agent into the biological structure in a liquid at a constant pressure.

78. A method of increasing a size of a body duct or viscus, comprising forming an isolated chamber within the body duct or viscus, and introducing fluid under pressure into the isolated chamber to increase the size.